Docket No. 434-204

Patent

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RP
5603

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

THOMAS G. BURKE ET AL.

Serial No.: 09/807,332

Filing Date: May 21, 2001

For: OLIGONUCLEOTIDE DELIVERY SYSTEMS FOR CAMPTOTHECINS

Group Art Unit: 1632

Examiner: Nguyen, David Trong

RESPONSE

Assistant Commissioner
for Patents
Washington, D.C. 20231

Sir:

The Applicants now respond to the Office Action of December 18, 2002 by traversing the rejection of the claims without making any amendment to the claims.

The Applicants note the rejection of claims 10, 15, 18 and 24 under 35 U.S.C. §112, first paragraph, for non-enablement. The Applicants believe that if the Examiner carefully reviews and considers the specification from, for example, page 25 line 7 to page 26 line 6 and from page 27 line 14 to page 37 line 23 the Examiner will agree that sufficient guidance is provided in the specification in order to provide enablement to these claims in accordance with the requirements of 35 U.S.C. §112. Accordingly, the Examiner is respectfully requested to withdraw this rejection to these claims.

Claims 18-21 also very clearly patentably distinguish over the Strode et al. article entitled "DNA Interactions of Two Clinical Camptothecin Drugs Stabilize Their Active Lactone Forms". More specifically, claim 18 reads on a chemotherapeutic composition comprising an oligonucleotide-camptothecin drug complex including a pharmaceutically effective amount of active lactone camptothecin drug that dissociates from the oligonucleotide within the body and exerts therapeutic activity. While the Strode reference illustrates that active lactone forms of CPT-11 and TPT are stabilized through interactions with double-stranded DNA, the Strode reference plainly does not teach or suggest the chemotherapeutic composition claimed.

More specifically, Strode does not suggest that any duplex of DNA oligonucleotides and camptothecin agents will be useful in the treatment of cancer nor does it teach a composition including a pharmaceutically effective amount of active lactone camptothecin drug as claimed in claim 18 or claims 19-21 dependent therefrom. In fact, with regard to claim 20, Strode actually teaches away from the claimed invention since Strode states that single strand DNA "showed significantly diminished effects on stabilizing both TPT and CPT-11" (see page 2980, column 1 lines 25-27).

Claims 18-21 also patentably distinguish over the Chourpa et al. article entitled "SERS and Fluorescence Study of the Molecular Interactions of Camptothecins with DNA and DNA Topoisomerase I and in Their Ternary Cleavable Complexes." This reference does disclose that an important structural requirement for camptothecin

efficacy is the hydrolysable α-hydroxy-lactone ring of these drugs.

While Chourpa notes a ratio-dependent stabilization of the lactone forms of camptothecins in the presence of an excess of oligonucleotide 1 or oligonucleotide 2, such stabilization did not occur for oligonucleotide 3. Thus, the results for oligonucleotide 3 actually teach away from the present invention. Further, Chourpa in no way teaches or suggests the provision of a chemotherapeutic composition comprising an oligonucleotide camptothecin drug complex including a pharmaceutically effective amount of active lactone camptothecin drug that dissociates from the oligonucleotide within the body and exerts therapeutic activity as set forth in claim 18. This aspect of the present invention is neither disclosed, taught or suggested in the cited reference. As such, claim 18 as well as claims 19-21 dependent thereon patentably distinguish over the Chourpa et al. article and should be allowed.

Claims 9-13, 18-22, 24 and 25 also patentably distinguish over U.S. Patent 5,583,034 to Green when considered in combination with either the Strode et al. or Chourpa et al. articles and U.S. Patent 5,834,012 to Perez-Soler et al.

While the Applicants note the references to oligonucleotides and camptothecin in the Green et al. patent at columns 6, 8 and 9 as noted by the Examiner, column 9 lines 11-19 explicitly provides that the antisense oligonucleotide and the therapeutic agent are provided as a mixture. In a true chemical sense, a mixture is not a complex as claimed in the present invention and, accordingly, the present invention distinguishes from this

reference. Stated another way, the Green et al. reference does not teach or suggest a camptothecin-oligonucleotide complex where a key function of the nucleotide is to maintain the active lactone form of the camptothecin. In the pharmaceutical compositions taught by Green et al., conditions are not conducive to stabilizing the active lactone form of the camptothecin and the invention as claimed is simply not disclosed. Further, the secondary references to Strode et al., Chourpa et al. and Perez-Soler et al. fail to provide the missing teaching. Specifically, whether considered alone or in combination, the references do not teach or suggest the invention as set forth in claims 9-13, 18-22, 24 and 25. Accordingly, these claims patentably distinguish over this art and should be allowed.

Claims 10, 14, 18 and 22 also patentably distinguish over the Green et al. reference when considered in combination with either the Strode et al. or Chourpa et al. reference in further combination with the Matteucci et al. reference entitled "Sequence-Specific Targeting of Duplex DNA Using a Camptothecin-Triple Helix Forming Oligonucleotide Conjugate and Topoisomerase I". As noted above, the primary reference to Green et al. refers to a mixture of camptothecin and oligonucleotide and not a complex as claimed. Such a mixture does not function to stabilize the active lactone form of the camptothecin. This is clearly evidence when one reviews the work of the Green et al. reference wherein stock solutions of camptothecins were made up in DMSO in the absence of oligonucleotide and these solutions were then diluted into aqueous

media. In Green et al., the direct complexation of camptothecin and resultant stabilization of the active lactone is not described, nor is it achieved and it is not obvious from the described formulation that camptothecin lactone stabilization by complexing with oligonucleotide would occur. Again, as noted above, the secondary references do not provide the missing teaching and, accordingly, claims 10, 14, 18 and 22 patentably distinguish over this art and should be allowed.

Finally, claims 18 and 20 are patentable over the Chourpa et al. reference when considered in combination with the Matteucci et al. reference. As noted above, the Chourpa et al. reference fails to suggest that an oligonucleotide-camptothecin drug complex is useful as a chemotherapeutic composition or that any such composition should be prepared including a pharmaceutically effective amount of active lactone camptothecin drug that dissociates from the oligonucleotide within the body and exerts therapeutic activity as set forth in claim 18 or claim 22 dependent thereon. Further, while the Matteucci et al. reference does suggest that you may use a covalent bond to conjugate a camptothecin to an oligonucleotide, it does not suggest in combination with the Chourpa reference that an oligonucleotide-camptothecin drug complex may be utilized in a chemotherapeutic composition much less that the camptothecin drug may be metabolically released from the oligonucleotide within the body as claimed. Thus, claims 18 and 22 also patentably distinguish over this art and should be formally allowed.

Finally, the Applicants note the objection to the drawing figures. The Applicants agree to provide revised drawing figures fully meeting the requirements of the Patent and Trademark Office but request that the Examiner hold that requirement in abeyance until such time as allowable subject matter is indicated.

In summary, all the pending claims patentably distinguish over the art and upon careful review and consideration of these comments and the full disclosure presented in the patent application, it is believed that the Examiner will agree with this proposition. Accordingly, the early issue of a formal Notice of Allowance is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on April 25, 2003

Date 04-25-2003 Carolina Perdomo